LEXSEE 2004 US DIST LEXIS 10

PURDUE PHARMA L.P., THE PURDUE FREDERICK COMPANY, THE P.F. LABORATORIES, INC., THE PURDUE PHARMA COMPANY, Plaintiffs and Counterclaim Defendants, -against - ENDO PHARMACEUTICALS INC., Defendant and Counterclaim Plaintiff, ENDO PHARMACEUTICALS HOLDINGS INC., Defendant, v. EUROCELTIQUE S.A., Counterclaim Defendant.

00 Civ. 8029 (SHS), 01 Civ. 2109 (SHS), 01 Civ. 8177 (SHS)

UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF NEW YORK

2004 U.S. Dist. LEXIS 10*; *70 U.S.P.Q.2D (BNA) 1185

January 5, 2004, Decided
January 5, 2004, Filed

SUBSEQUENT HISTORY: Motion denied by *Purdue Pharma L.P. v. Endo Pharms., Inc., 2004 U.S. Dist. LEXIS 2276 (S.D.N.Y., Feb. 13, 2004)*
Motion granted by, Dismissed by, in part, Motion denied by *Purdue Pharma L.P. v. Endo Pharms., Inc., 102 Fed. Appx. 725, 2004 U.S. App. LEXIS 14541 (Fed. Cir., 2004)*
Affirmed by *Purdue Pharma L.P. v. Endo Pharms., Inc., 410 F.3d 690, 2005 U.S. App. LEXIS 10416 (Fed. Cir., 2005)*
Related proceeding at *Jolly v. Purdue Pharma L.P., 2005 U.S. Dist. LEXIS 44599 (S.D. Cal., Sept. 27, 2005)*
Affirmed in part and vacated in part by, Remanded by, On rehearing at *Purdue Pharma L.P. v. Endo Pharms., Inc., 438 F.3d 1123, 2006 U.S. App. LEXIS 2887 (Fed. Cir., 2006)*
Vacated by, in part, Reconsideration granted by *Purdue Pharma L.P. v. End0 Pharms., 2006 U.S. Dist. LEXIS 15321 (S.D.N.Y., Mar. 29, 2006)*
Related proceeding at *Rite Aid Corp. v. Purdue Pharma, L.P., 2007 U.S. Dist. LEXIS 61583 (S.D.N.Y., Aug. 21, 2007)*

DISPOSITION: [*1] Patent claims against Endo were dismissed, patents 5,549,912, 5,508,042 and 5,656,295 were infringed and declared invalid and Purdue was enjoined from enforcing those patents.

COUNSEL: For Purdue Pharma LP, The Purdue Frederick Company, The PF Laboratories, Inc, The Purdue Pharma Company, PLAINTIFFS (1:00cv8029): Herbert F Schwartz, Richard A. Inz, Robert J. Goldman, Fish & Neave, New York, NY; Kelsey I. Nix, Willkie Farr & Gallagher LLP (NY), New York, NY.

For Endo Pharmaceuticals Inc, Endo Pharmaceuticals Holding Inc, DEFENDANTS (1:00cv8029): Albert B. Chen, Donald Luther Rhoads, Louis H. Weinstein, Michael S. Oberman, Nicholas L. Coch, Robert Alderson, Kramer Levin Naftalis & Frankel, LLP, New York, NY; Edward V Eilardi, Constance S. Huttner, Douglas R. Nemee, Skadden, Arps, Slate, Meagher & Flom, LLP, New York, NY.

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For Purdue Pharma LP, The Purdue Frederick Company, The PF Laboratories, Inc, The Purdue Pharma Company, COUNTER DEFENDANTS (1:00cv8029): Herbert F Schwartz, Richard A. Inz, Robert J. Goldman, Fish & Neave, New York, NY; Kelsey I. Nix, Willkie Farr & Gallagher LLP (NY), New York, NY.

JUDGES: SIDNEY H. STEIN, U.S. District Judge.

OPINION BY: SIDNEY H. STEIN

OPINION

OPINION AND ORDER

SIDNEY H. STEIN, U.S. District Judge.

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I. Introduction

Plaintiffs Purdue Pharma, L.P., the Purdue Frederick Company, the P.F. Laboratories, Inc. and the Purdue Pharma Company (collectively, "Purdue") bring this patent action pursuant to *35 U.S.C. § 271(e)(2)*, alleging that defendants Endo Pharmaceuticals Inc. and Endo Pharmaceuticals Holdings Inc. (collectively, "Endo") infringed Purdue's patents protecting its product OxyContin -- a controlled release oxycodone analgesic designed to treat moderate to severe pain.

Purdue filed suit against Endo pursuant to the procedures set forth in the Hatch-Waxman Act, codified in the Food and Drug Act at *21 U.S.C. § 355 et seq.*, and incorporated into the patent statute at *35 U.S.C. § 271(e)(2)*. The [*3] Hatch-Waxman Act permits an applicant to file an Abbreviated New Drug Application ("ANDA") with the Food and Drug Administration ("FDA") requesting approval of a bioequivalent ("generic") version of a drug that is already listed by the FDA as approved for safety and effectiveness without having to submit additional safety and efficacy data. See *21 U.S.C. § 355(j)(2)(A)*. However, the applicant must certify with respect to any relevant patents for the listed drug that it will either not market its drug prior to the relevant patent's expiration, or that the relevant patents "[are] invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the [ANDA] is submitted." *21 U.S.C. § 355(j)(2)(A)(vii)(IV)*. If the applicant makes the latter certification, it must notify the holder of the patent, who may then timely sue the applicant for infringement pursuant to *35 U.S.C. § 271(e)(2)*. See *21 U.S.C. § 355 (j)(2)(B)(i), (j)(5)(B)(iii)*.

In 2000, Endo filed ANDA No. 75-923, subsequently twice amended in 2001, and correspondingly provided Purdue with notices that [*4] it was seeking FDA approval of various dosage strengths of oxycodone hydrochloride extended-release tablets and that it had certified to the FDA that Purdue's relevant patents either (1) would not be infringed or (2) were invalid. Purdue timely filed suit for patent infringement, alleging that Endo's submission of ANDA No. 75-923 violated claims 1-4 of *U.S. Patent No. 5,549,912*, claims 1 and 2 of *U.S. Patent No. 5,508,042* and claims 1-4 and 6-10 of *U.S. Patent No. 5,656,295* (each of these patents is assigned to counterclaim defendant Euroceltique S.A.). Purdue also seeks recovery of attorneys fees pursuant to *35 U.S.C. §§ 271(e) and 285*. Endo Pharmaceuticals Inc. has filed counterclaims against Purdue and Euroceltique seeking a declaration that the patents in suit are invalid and unenforceable and that Purdue's misuse of these patents violated federal antitrust laws, as well as injunctive relief and damages. On July 31, 2002, the FDA gave tentative approval to Endo's proposed 10 mg, 20 mg, 40 mg and 80 mg products.

Prior to trial, this Court consolidated the above-captioned actions and bifurcated the trial of defendants' antitrust counterclaims from the trial [*5] on the patent issues. See Order dated May 7, 2002; Order dated December 10, 2002. The patent issues were tried to this

Court without a jury over the course of several weeks in June 2003. After consideration of all the evidence, this Court finds that Purdue has proven by a preponderance of the evidence that Endo infringed its patents, but Endo has proven by clear and convincing evidence that the patents are invalid due to Purdue's inequitable conduct before the Patent and Trademark Office (the "PTO") during the prosecution of the patents in suit.

II. Background [1]

1 In a prior action, Purdue sued Roxanne Laboratories, Inc. and its related companies for violating the patents in suit in the present action. See Purdue v. Boehringer Ingelheim GMBH, No. 99 Civ. 3658. This Court granted Purdue's motion for a preliminary injunction barring Boehringer from making, using, or offering to sell "Roxicodone SR," a controlled release oxycodone analgesic product, a result that the Federal Circuit affirmed. See *Purdue v. Boehringer, 98 F. Supp. 2d 362, 400 (S.D.N.Y. 2000)*, aff'd *237 F.3d 1359 (Fed. Cir. 2001)*.

[*6] A. The Purdue Patents

1. The Parent Patent: The '331 Patent

Purdue filed Patent No. 5,266,331 (the "'331 patent") on November 27, 1991 and it issued on November 30, 1993. Although Purdue is not asserting any of the '331 patent claims against Endo as a basis for finding infringement, this patent is significant to this litigation in that it is the parent application of the patents in suit - all three patents in suit derived as continuations of the '331 patent. [2] The '331 patent lists Benjamin Oshlack, John J. Minogue and Mark Chasin as the inventors.

2 "In general, a continuing application [either a continuation, divisional or continuation-in-part application] is one filed during the pendency of another application which contains at least part of the disclosure of another application and names at least one inventor in common with that application .... A "continuation" application claims the same invention claimed in an earlier invention, although there may be some variation in the scope of the subject matter claimed ... the divisional application claims only one or more, but not all, of the independent inventions of the earlier application. A [continuation-in-part] application ... contains a portion or all of the disclosure of an earlier application together with added matter not present in that earlier application." *Transco Prods. Inc. v. Performance Contracting, Inc., 38 F.3d 551, 555-56 (Fed. Cir. 1994)*.

[*7] 2. The *'912 Patent*

Purdue filed Patent No. 5,549,912 (the "*'912 patent*") - a continuation-in-part of the '331 patent - on November 25, 1992 and it issued on August 27, 1996. The *'912 patent*, like the other two patents in suit, list Benjamin Oshlack, John J. Minogue, Mark Chasin and Robert F. Kaiko as the inventors. Claims 1 to 4 of the *'912 patent* state:

1. A controlled release oxycodone formulation for oral administration to human patients, comprising from about 10 to about 40 mg oxycodone or a salt thereof, said formulation providing a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

2. A controlled release oxycodone formulation for oral administration to human patients, comprising from about 10 mg to about 160 mg oxycodone or a salt thereof, said formulation providing a mean maximum plasma concentration of oxycodone from about 6 to about 240 ng/ml from a mean of about 2 to about [*8] 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 120 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

3. A solid controlled release oral dosage form, comprising (a) oxycodone or a salt thereof in an amount from 10 to about 160 mg; (b) an effective amount of a controlled release matrix selected from the group consisting of hydrophilic polymers, hydrophobic polymers, digestible substituted or unsubstituted hydrocarbons having from about 8 to about 50 carbon atoms, polyalkylene glycols, and mixtures of any of the foregoing; and (c) a suitable amount of a suitable pharmaceutical diluent, wherein said composition provides a mean maximum plasma concentration of oxycodone from about 6 to about 240 ng/ml from a mean of about 2 to about 4.5

hours after administration, and a mean minimum plasma concentration from about 3 to about 120 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

4. The controlled release composition of claim 3, wherein said controlled release matrix comprises an acrylic [*9] resin.

3. The *'042 Patent*

Patent No. 5,508,042 (the '*"042 patent*") - a divisional of the *'912 patent* - was filed on June 6, 1995 and issued April 16, 1996. Claims 1 and 2 of the *'042 patent* mirror claims 1 and 2 of the *'912 patent*, and read as follows:

1. A method for reducing the range in daily dosages required to control pain in human patients, comprising administering an oral controlled release dosage formulation comprising from about 10 to about 40 mg oxycodone or a salt thereof which provides a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-conditions.

2. A method for reducing the range in daily dosages required to control pain in substantially all human patients, comprising administering an oral solid controlled release dosage formulation comprising from about 10 mg to about 160 mg oxycodone or a salt thereof which provides a mean maximum plasma concentration of oxycodone up to about 240 [*10] ng/ml from a mean of up to about 2 to about 4.5 hours afer administration, and a mean minimum plasma concentration up to about 120 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

4. The *'295 Patent*

Patent No. 5,656,295 (the '*"295 patent*") - a continuation in part of the *'912 patent* - was filed on March 19, 1996 and issued August 12, 1997. Claims 1 to 4 and 6 to 10 read as follows:

1. A controlled release oxycodone formulation for oral administration to human patients, comprising from about 10 mg to about 160 mg oxycodone, based on the hydrochloride salt, said formulation providing a mean maximum plasma concentration of oxycodone from about 6 to about 240 ng/ml from a mean of about 2 to about 4.5 hours after administration and a mean minimum plasma concentration of oxycodone from about 3 to about 120 ng/ml from about 10 to about 14 hours after administration every 12 hours after repeated dosing through steady state conditions, wherein said formulation provides pain relief in said patient for at least 12 hours after administration.

2. The controlled release oxycodone formulation of [*11] claim 1, comprising from about 10 to about 40 mg oxycodone based on the hydrochloride salt, said formulation providing a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration.

3. The controlled release oxycodone formulation of claim 1, comprising from about 40 mg to about 160 mg oxycodone based on the hydrochloride salt, said formulation providing a mean maximum plasma concentration of oxycodone from about 60 to about 240 ng/ml from a mean of about 2 to about 4.5 hours after administration.

4. The solid controlled release oxycodone formulation of claim I, comprising oxycodone hydrochloride dispersed in an effective amount of a controlled release matrix selected from the group consisting of hydrophilic polymers, hydrophobic polymers, digestible substituted or unsubstituted hydrocarbons having from about 8 to about 50 carbon atoms, polyalkylene glycols, and mixtures of any of the foregoing, and a suitable amount of a suitable pharmaceutical diluent.

6. The controlled release oxycodone formulation of claim 1, comprising a tablet wherein said oxycodone is dispersed in a controlled release [*12] matrix.

7. The controlled release oxycodone formulation of claim 1, wherein said oxycodone is in the form of the hydrochloride salt.

8. A method for substantially reducing the range in daily dosages required to control pain in human patients, comprising administering to a human patient an oral controlled release dosage formulation comprising from about 10 to about 160 mg oxycodone or a salt thereof based on the hydrochloride salt which provides a mean maximum plasma concentration of oxycodone form (sic) about 6 to about 240 ng/ml from a mean of about 2 to about 4.5 hours after administration and a mean minimum plasma concentration of oxycodone from about 3 to about 120 ng/ml from about 10 to about 14 hours after administration every 12 hours after repeated dosing through steady state conditions, wherein said formulation provides pain relief in said patient for at least 12 hours after administration.

9. A method for substantially reducing the range in daily dosages required to control pain in substantially all human patients, comprising administering to a human patient an oral solid controlled release dosage formulation comprising from about 10 mg to about 40 mg oxycodone [*13] or a salt thereof based on the hydrochloride salt which provides a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of up to about 2 to about 4.5 hours after administration and a mean minimum plasma concentration of oxycodone from about 3 to about 30 ng/ml from about 10 to about 14 hours after administration every 12 hours after repeated dosing through steady state conditions, wherein said formulation provides pain relief in said patient for at least 12 hours after administration.

10. A method for substantially reducing the range in daily dosages required to control pain in substantially all human patients, comprising administering to a human patient an oral solid controlled release dosage formulation comprising from about 40 mg to about 160 mg oxycodone or a salt thereof based on the hydrochloride salt which provides a mean maximum plasma concentration of oxycodone from about 60 to about 240 ng/ml from a mean of up to about 2 to about 4.5 hours after administration and a mean minimum plasma concentration of oxycodone from about 30 to about 120 ng/ml from about 10 to about 14 hours after administration after repeated dosing every 12 hours [*14] through steady state conditions, wherein said formulations provides pain relief in said patient for at least 12 hours after administration.

B. Terminology

Drugs known as opioid analgesics include morphine, hydromorphone, and oxycodone - the active ingredient in OxyContin - and are generally used to treat moderate to severe pain. "Pharmacokinetics" refers to the blood plasma concentration of a drug in the body over time. Tr. 86. [3] The pharmacokinetic symbols used in this opinion are as follows: "C" is a shorthand for concentration, "T" for time, "max" for maximum and "min" for minimum. Therefore, "C[max]" is the mean peak blood plasma concentration exhibited by the claimed oxycodone formulations, "T[max]" is the time that C[max] occurs, "C[min]" is the mean minimum blood plasma concentration and "T[min]" is the time that C[min] occurs. A drug formulation is a combination of a biologically active ingredient and excipients - pharmacologically inert ingredients that are not active in the body. Tr. 465-66. Drug formulations are tested through both "in vitro" and "in vivo" testing. In vitro testing examines the rate a drug tablet dissolves in special laboratory apparatuses. [*15] Tr. 470-71. In vivo testing is testing of the drug in humans. Titration is the method by which dosages are adjusted in order to provide acceptable pain control without unacceptable side effects. Tr. 99, 169, 1233. "Steady state" refers to the repeated dosing of a drug until it reaches a stable level of absorption and elimination such that the amount of drug in the body is constant. Tr. 1249. Bioequivalence means that the "rate and extent of absorption of the [generic] drug does not show a significant difference from the rate and extent of absorption" of the reference drug. *21 U.S.C. § 355(j)(8)(B)(i)*. "Bioavailability" refers to the degree to which a drug is absorbed in the body, for example, "high oral bioavailability" mean that a large por-

tion of an orally administered dosage is absorbed in the bloodstream. Tr. 95-6.

3 "Tr. _" refers to the relevant page of the transcript of the trial of this action; "PTX " refers to plaintiffs' relevant exhibit; "DX _" refers to defendants' relevant exhibit.

[*16] III. Discussion

A. Infringement

Determining patent infringement in an ANDA action is no different from determining patent infringement in a non-ANDA action, although the statute requires an infringement inquiry focused on what is likely to be sold following FDA approval, since the allegedly infringing product is not being sold commercially. See *Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1568 (Fed. Cir. 1997)*. Purdue bears the burden of proving infringement by a preponderance of the evidence. See *Advanced Cardiovascular Sys. Inc. v. Scimed Life Sys. Inc., 261 F.3d 1329, 1336 (Fed. Cir. 2001)*. "A two-step process is used in the analysis of patent infringement: first, the scope of the claims are determined as a matter of law, and second, the properly construed claims are compared to the allegedly infringing device to determine, as a matter of fact, whether all of the limitations of at least one claim are present, either literally or by a substantial equivalent, in the accused device." *Teleflex, Inc. v. Ficosa North America Corp., 299 F.3d 1313, 1323 (Fed. Cir. 2002)* (citations omitted); see also *Merck & Co. v. Teva Pharms. USA, Inc., 347 F.3d 1367, 1369 (Fed. Cir. 2003)*.

[*17] 1. Claim Construction

"It is the claims that measure the invention." *Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1325 (Fed. Cir. 2003)* (quoting *SRI Int'l v. Matsushita Elec. Corp., 775 F.2d 1107, 1121 (Fed. Cir. 1985)* (en banc)). The first step in claim construction is to determine the ordinary and customary meaning, if any, that would be attributed to the term by those skilled in the art. See *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 320 F.3d 1339, 1347 (Fed. Cir. 2003)*. Neither party contests that one skilled in the art would be an individual with some education in biology or chemistry, or with a pharmaceutical background, with some experience with controlled-release formulations. Tr. 1207-08, 1469. "In the absence of an express intent to impart a novel meaning to claim terms, an inventor's claim terms take on their ordinary meaning." *Teleflex, 299 F.3d at 1325-26* (citation omitted). There is a "heavy presumption" that the terms used in the claim carry their ordinary and customary meaning. *CCS Fitness, Inc. v. Brunswick Corp., 288 F.3d 1359, 1366 (Fed. Cir. 2002)*. [*18]

The specification is also "highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Teleflex, 299 F.3d at 1325* (citing *Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996))*. "One purpose for examining the specification is to determine if the patentee has limited the scope of the claims." *Watts v. XL Sys, 232 F.3d 877, 882 (Fed. Cir. 2000)*. The prosecution history may also "demonstrate that the patentee intended to deviate from a term's ordinary and accustomed meaning, i.e., if it shows the applicant characterized the invention using words or expressions of manifest exclusion or restriction during the administrative proceedings before the Patent and Trademark Office." *Teleflex, 299 F.3d at 1326*.

If the meaning of a term is unclear from the claims, specification and prosecution history, a court may rely on extrinsic evidence such as expert or inventor testimony, dictionaries and learned treatises. See *Key Pharms. v. Hercon Lab. Corp., 161 F.3d 709, 716 (Fed. Cir. 1998)* (citing *Markman v. Westview Instruments, Inc., 52 F.3d 967, 980 (Fed. Cir. 1995))*. [*19] Extrinsic evidence "cannot change the meaning of a term as used in the claim from the meaning with which it is used in the specification. However, it is not prohibited to provide the opinions and advice of experts to explain the meaning of terms as they are used in patents and as they would be perceived and understood in the field of an invention." *Merck, 347 F.3d at 1372* (citing *Omega Eng'g, Inc. v. Raytek Corp., 334 F.3d 1314, 1332 (Fed. Cir. 2003)*; *Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1309 (Fed. Cir. 1999))*. Additionally, the testimony of the inventors against their own interest is relevant and persuasive to inform the court's claim construction. See *Evans Med. Ltd. v. American Cyamid Co., 11 F. Supp. 2d 338, 350 (S.D.N.Y. 1998)*, aff'd, *215 F.3d 1347 (Fed. Cir. 1999)*.

Since the *'042 patent* is a divisional of, and the *'295 patent* is a continuation-in-part of, the *'912 patent*, which is itself a continuation-in-part of the '331 patent, and the patents in suit have identical disclosures, claim limitations may also be derived from the prosecution history of the '331 patent. See *Omega, 334 F.3d at 1333*; [*20] *Advanced Cardiovascular Systems, Inc. v. Medtronic, Inc., 265 F.3d 1294, 1305 (Fed. Cir. 2001)* ("the prosecution history of a related patent can be relevant if, for example, it addresses a limitation in common with the patent in suit"); *Elkay Mfg. Co. v. Ebco Mfg. Co., 192 F.3d 973, 980 (Fed. Cir. 1999)* ("when multiple patents derive from the same initial application, the prosecution history regarding a claim limitation in any patent that has issued applies with equal force to subsequently issued

patents that contain the same claim limitation"); *Jonsson v. Stanley Works, 903 F.2d 812, 818 (Fed. Cir. 1990)* (prosecution of parent application is relevant to understanding scope of claims issuing in a continuation-in-part application).

a. C[min]

The first claim construction dispute centers around the method for calculating C[min], the mean minimum plasma concentration. Endo contends that C[min] would be calculated by those skilled in the art by taking each patient's minimum concentration, at whatever time it was reached, totaling up those numbers for all patients, and dividing by the number of patients. Purdue, on the other [*21] hand, contends that the claims should not be limited to a particular method for measuring C[min]. It argues that C[min] could be measured as Endo contends, or it could be measured at C,[2], the end of a dosing interval during steady state for a 12-hour formulation, or C[min] could also be properly measured as the average of the plasma levels at T[0] and T[I2].

In resolving this dispute, this Court turns first to the language of the claims themselves. The '912, '042 and *'295 patents* claim a mean minimum plasma concentration up to 120 ng/ml "from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions." *'912 patent*, claims 1-3; *'042 patent*, claims 1-2; *'295 patent*, claims 1, 8-10. This language does not provide a method for calculating C[min], although it does state in ordinary language that the range for C[min] occurs between 10 and 14 hours after achieving steady-state conditions.

Because the claim language does not provide a method for calculating C[min], we next look to the specifications in the patents in suit. Purdue contends that Example 18 of the *'912 patent* computed C[min] by taking the average of [*22] the plasma levels at T[0] and T[I2], which, at steady state, represent the end of two dosing intervals for a 12-hour drug formulation. However, no method for calculating C[min] is provided in Example 18 of the *'912 patent*, or in any other part of the specifications for the '912, '295 or *'042 patents*. Therefore, the specifications fail to shed light as to how to calculate C[min]. The prosecution histories are similarly devoid of any indication of how to calculate C[min].

Since neither the claim language nor the specifications nor the prosecution histories provide guidance on how to calculate C[min], this Court looks to extrinsic evidence to determine how those of ordinary skill in the art would have calculated C[min] at the time the patents were filed. See *Key Pharm., 161 F.3d at 716*. Endo's claim construction expert, Dr. Sanford Bolton, testified that the mean minimum plasma concentration is calculated by looking over "a dosing interval at steady state and look at the various concentrations at the blood sampling times, and for each patient or subject in the study obtain a minimum value, and then average those minimum values." Tr. 1469. Dr. Donald Stanski, [*23] Purdue's claim construction expert, and Dr. Paul D. Goldenheim, Purdue's executive vice president of research and development and chief scientific officer, both testified that C[min] could be calculated at C[12], the end of a dosing interval for a 12-hour formulation at steady state, or the average of C[0] and C[12] - both of which occur immediately before dosing at steady state. Tr. 652; Tr. 976-77. Dr. Robert F. Kaiko, a named inventor of all of the patents in suit, testified that he calculated C[min] in the same manner suggested by Dr. Bolton, namely by adding the "lowest oxycodone concentration" of each of the subjects of the study divided by the number of subjects in the study. Tr. 216. However, Dr. Kaiko utilized a different method for calculating C[min] in a 1996 published paper he coauthored which defined C[min] as the "average of the 0- and 12-hour plasma oxycodone concentrations." PTX 563, P645913.

Additionally, the FDA's July 1992 guidelines, applicable in November 1992 when Purdue filed the *'912 patent*, states that C[min] defined as "the drug concentrations at the end of each dosing interval during steady state." PTX 916. Consequently, pursuant to the FDA [*24] guidelines, C[min] would be C[12] for a 12-hour formulation.

This Court finds Purdue's argument persuasive. A review of the patents' claims, specifications and prosecution histories reveals only that C[min] is measured between 10 and 14 hours after achieving steady state conditions. There is no indication from the intrinsic evidence as to how C[min] should be measured. The extrinsic evidence presented by the parties indicates that one of ordinary skill in the art could use several different methods to calculate C[min] when the patents were filed. Since measurement of C[12] occurs 12 hours after dosing, and the claimed mean minimum plasma concentration is measured between the range of 10 to 14 hours, C[12] (and correspondingly T[12]) falls within the range of 10 to 14 hours - therefore, the claims do not exclude using C[I2] as C[min]. Measuring C[min] as the average of C[0] and C[12] for a 12-hour formulation also falls within the claimed range since C[0] is at the end of a dosing interval during steady state and C[12] is the end of the subsequent dosing interval. Accordingly, this Court will not "import into the claims limitations that were unintended [*25] by the patentee." *Amgen, 314 F.3d at 1325*; *LNP Eng'g Plastics, Inc. v. Miller Waste Mills, Inc., 275 F.3d 1347, 1353-56 (Fed. Cir. 2001)*. One skilled in the art would not limit measurements of C[min] to the sole method proposed by Endo.

b. Controlled release

The second claim construction dispute centers around the meaning of the term "controlled release." Endo contends that "controlled release" should be construed to require reduced dosage range and easier titration. Purdue contends that "controlled release" means that the dosage form is designed so that the active ingredient - oxycodone - releases in a controlled manner over an extended period of time, in contrast to "immediate release" where the release rate of the active ingredient is not controlled.

Looking to the claim language itself, the term "controlled release" oxycodone formulation is used in Claims 1 and 2 of the'912, '042 and *'295 patents* to describe formulations that result in a mean maximum plasma concentration between 2 and 4.5 hours after administration and a mean minimum plasma concentration from 10 to 14 hours after repeated administration every 12 hours through steady-state [*26] conditions. See also the *'295 Patent*, Claims 3, 8-10. None of the bodies of the claims disclose a reduced dosage range or easier titration. Accordingly, as inferred from how the term is used in the claims, the ordinary meaning of "controlled release" is consistent with Purdue's interpretation - that is, "controlled release" is the release of oxycodone in a controlled manner over an extended period of time.

The preamble to Claim 8 of the *'295 Patent* reads, "[a] method for substantially reducing the range in daily dosages required to control pain in human patients, comprising ..." and the preambles to the *'042 patent* claims both read, "[a] method for reducing the range in daily dosages required to control pain in human patients, comprising ...." However, Endo does not contend that the preambles should be read as imposing limitations on either the claims generally or on the specific term "controlled release." Accordingly, this Court shall not revisit its earlier finding in Purdue v. Boehringer - made in the context of granting a preliminary injunction - that the preambles in the patents in suit do not state independent limitations of the claimed inventions. See *Boehringer, 98 F. Supp. 2d at 377.* [*27] Some of the claims do set forth a range of dosages, see, e.g., Claim 1 of the *'912 patent*, which states "[a] controlled release oxycodone formulation for oral administration to human patients, comprising from about 10 to about 40 mg oxycodone or a salt thereof," but this language merely states a dosage range, not a reduced dosage range. Therefore, according to the customary and ordinary language of the claims, "controlled release" does not require reduced dosage ranges or ease of titration limitations.

Turning to the specifications of the patents in suit, the term "controlled release" is used consistent to how it is used in the claims - specifically, "controlled release" is described as the release of oxycodone in a controlled manner over an extended period of time. For example, Examples 1-4 of each of the patents in suit describe "controlled release" tablets in the context of the dissolution rates of oxycodone over an extended period of time. See the '912, '295 and *'042 Patents*, Tables 2, 4, 6 and 8. Similarly, Figure 5 of the patents in suit charts the plasma concentration over "time from last dose" and is described as a graph "showing the mean plasma concentration for [*28] a 10 mg controlled release oxycodone formulation ...." '912 and *'295 Patents*, Cols. 3:27-30; *'042 Patent*, 3:31-34.

However, as this Court previously noted in Boehringer, the specifications also "repeatedly refer to a reduction in the range of daily dosages." *98 F. Supp. 2d at 377.* For example, the section of the specifications entitled "Detailed Description" opens with the following passage,"it has now been surprisingly discovered that the presently claimed controlled release oxycodone formulations acceptably control pain over a substantially narrower, approximately four-fold (10 to 40 mg every 12 hours - around-the-clock-dosing) in approximately 90% of patients for opioid analgesics in general." *'912 patent*, 3:34-41; *'042 Patent*, 3:38-45; *'295 Patent*, 3:34-41. See also *'912 Patent*, 3:67 to 4:8, 1:10-45; *'042 Patent*, 2:16-20, 3:5-22; *'295 Patent*, 2:3-17, 3:1-18. The specifications also state that "the use of from about 10 mg to about 40 mg of 12-hourly doses of controlled-release oxycodone to control pain in approximately 90% of patients ... is an example of the unique characteristics of the present invention." *'912 Patent*, 3:42-46; *'042 Patent*, 3:46-51; *'295* [*29] *Patent*, 3:42-47. Further on, the specifications state that,

> the clinical significance provided by the controlled release oxycodone formulations of the present invention at a dosage range from about 10 to about 40 mg every 12 hours for acceptable pain management in approximately 90% of patients with moderate to sever pain, as compared to other opioid analgesics requiring approximately twice the dosage range provides for the most efficient and humane method of managing pain requiring repeated dosing.

'912 Patent, 4:51-57; *'042 Patent*, 4:53-60; *'295 Patent*, 4:51-58.

When read in their entirety, the specifications of the patents in suit indicate that the invention itself - the controlled release oxycodone formulation - may be limited to a four-fold dosage range that controls pain for 90% of

patients, but it does not indicate that the specific term "controlled release" by itself should be construed to require reduced dosage and ease of titration, especially when the customary and ordinary meaning of the term clearly does not include or even suggest these limitations.

Finally, we turn to the prosecution history of the patents in suit to ascertain whether that history is [*30] consistent with our interpretation of the disputed claim language. Endo contends that Purdue successfully convinced the PTO that the reduced dosage range and easier titration features distinguished the patent claims from the prior art, and therefore cannot now disavow construing the term "controlled release" as requiring reduced dosage range and ease of titration. Purdue contends that the references in the prosecution histories to reduced dosage range and ease of titration relate to benefits of the inventions rather than to claim limitations.

"An inventor may use the specification and prosecution history to define what his invention is and what it is not - particularly when distinguishing the invention over prior art. 'Just as prosecution history estoppel may act to estop an equivalence argument under the doctrine of equivalents, positions taken before the PTO may bar an inconsistent position on claim construction under *§ 112*, P 6.'" See *Ballard Med. Prods. v. Allegiance Healthcare Corp., 268 F.3d 1352, 1359 (Fed. Cir. 2001)* (quoting *Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1457 (Fed. Cir. 1998))*. "That explicit arguments made during prosecution [*31] to overcome prior art can lead to narrow claim interpretations makes sense, because 'the public has a right to rely on such definitive statements made during prosecution.'" *Spectrum Int'l, Inc. v. Sterilite Corp., 164 F.3d 1372, 1378-79 (Fed. Cir. 1998)* (quoting *Digital Biometrics v. Identix, Inc., 149 F.3d 1335, 1347 (Fed. Cir. 1998))*. "Prosecution history may limit claim scope if the patentee disclaimed or disavowed a particular interpretation of the claims during prosecution. This principle does not, however, mean that any words appearing in the prosecution history but not in the issued claims are forever banished. The prosecution history inquiry asks not what words the patentee discarded, but what subject matter the patentee relinquished or disclaimed." *Abbott Labs. v. TorPharm, Inc., 300 F.3d 1367, 1372 (Fed. Cir. 2002)*; *Schumer v. Lab. Computer Sys., Inc., 308 F.3d 1304, 1313 (Fed. Cir. 2002)* ("the prosecution history limits even clear claim language so as to exclude any interpretation surrendered during prosecution, but only where the accused infringer can demonstrate that the patentee surrendered that interpretation [*32] with reasonable clarity and deliberateness"). Accordingly, at issue is whether or not Purdue clearly and deliberately disclaimed or surrendered controlled release oxycodone formulations that do not reduce the dosage range and ease titration such that the term "controlled release" must be construed to require reduced dosage range and ease of titration.

In addition, the Federal Circuit has repeatedly emphasized that claim language is to be interpreted in light of the "fundamental purpose and significance" of the invention, *Minnesota Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc., 976 F.2d 1559, 1566-67 (Fed. Cir. 1992)* and in a manner "consistent with and further[ing] the purpose of the invention," *CVI/Beta Ventures. Inc. v. Tura LP, 112 F.3d 1146, 1160 (Fed. Cir. 1997)*, cert. denied, *522 U.S. 1109, 118 S. Ct. 1039, 140 L. Ed. 2d 105 (1998)*. [4] Courts must review the entire prosecution history in construing claims. See *Eagle Comtronics, Inc. v. Arrow Commun. Labs., Inc., 305 F.3d 1303, 1315 (Fed. Cir. 2002)*.

4 Purdue cites to several Federal Circuit cases for the supposedly contrary proposition that it is error for this Court to consider the disputed issues in a lawsuit based on the differences between the claimed invention and the prior art. See *Jones v. Hardy, 727 F.2d 1524, 1528 (Fed. Cir. 1984)* ("in determining the obvious/nonobviousness issue, it is improper (even if erroneously suggested by a party) to consider the difference [between the invention and the art] as the invention"); *Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1383 (Fed. Cir. 1986)*; *Hodosh v. Block Drug Co., 786 F.2d 1136, 1143 n.5 (Fed. Cir. 1986)*. See also *Para-Ordnance Mfg., Inc. v. SGS Importers Int'l Inc., 73 F.3d 1085, 1087 (Fed. Cir. 1995)* (stating, in the context of an obviousness analysis, that "there is no legally recognizable 'heart' of the invention") (citing *W.L. Gore & Asoc., Inc. v. Garlock, Inc., 721 F.2d 1540, (Fed. Cir. 1983)*, cert, denied *469 U.S. 851, 83 L. Ed. 2d 107 (1984))*. However, these cases only state that, for purposes of a *35 U.S.C. § 103* obviousness analysis, it is inappropriate for a court to consider the difference between the invention and prior art as the invention itself - here, this Court is construing claims and, accordingly, must consider assertions Purdue made before the PTO to distinguish its invention from prior art. See, e.g., *Hockerson-Halberstadt, Inc. v. Avia Group Int'l, Inc., 222 F.3d 951, 956 (Fed. Cir. 2000)*.

[*33] After reviewing the prosecution history of the '331 parent patent and the patents in suit, this Court finds that Purdue surrendered, with deliberateness and clarity, controlled release oxycodone formulations that do not control pain over an approximately four-fold dosage range for approximately 90% of patients; in other words, we conclude that reduced dosage range is a claim

limitation. The PTO initially rejected the '331 patent claims pursuant to *35 U.S.C. § 103* because "it would have been obvious to one of ordinary skill in the art to use oxycodone" in place of the hydromorphone in the 4,990,341 patent (the "'341 patent") in view of the 4,861,598 patent (the "'598 patent"). DX 2008, EN205614, EN205615. In Purdue's response to the PTO's rejection, Purdue distinguished the '331 invention by stating that (1) prior art controlled release opioid analgesics had a wide range of dosages that "makes the titration process particularly time consuming and resource consuming," (2) but "it has now been surprisingly discovered" that the oxycodone formulation of the '331 patent "acceptably controls pain over a substantially narrower, approximately four fold (10 to 40 mg every [*34] 12 hours - around-the-clock dosing) in approximately 90% of patients," (3) "the opioid analgesic titration process" of the '331 invention is "substantially reduced through the efficiency of the controlled release oxycodone formulations of the present invention," and (4) that

> it is respectfully submitted that one skilled in the art *having knowledge of the controlled release oxycodone formulations of Goldie, et al.* [the '341 patent] would not be motivated to prepare controlled release oxycodone formulations in a dosage range from about 10 mg to about 40 mg, which formulations thereby acceptably control pain over a substantially narrower, approximately four-fold range in approximately 90% of patients. This is in sharp contrast to the approximately eight-fold range required for approximately 90% of patients utilizing controlled release hydromorphone, or controlled release opioid analgesics in general. One skilled in the art would certainly not arrive at this surprising result without the benefit of hindsight.

DX 2008, EN205621 dated October 22, 1992 - entitled "The Results Obtained by the Present Invention are Not Obvious From the Prior Art" (italics added).

[*35] In other words, Purdue admitted to the PTO that the cited prior art would teach a controlled release oxycodone formulation, but the particular controlled release oxycodone formulation of the '331 invention would, in contrast to other controlled release opioid drugs -and in contrast to the controlled release oxycodone formulations of the cited prior art - control pain over a four-fold dosage range for most patients. Purdue distinguished the claimed '331 invention over the prior art by setting forth what the invention did not cover - specifically, controlled release oxycodone formulations that did not control pain over a four-fold dosage range for most patients.

After the relevant claims of the '331 patent were again rejected for obviousness, the PTO scheduled an interview with Purdue after which the examiner noted that they "discussed nature of dissolution rate with regard to prior art. Applicant will submit proposed declaration supporting unobviousness and unexpected results. Terminal disclaimer will be filed. Favorable consideration will be given for the proposals discussed regarding allowability." PTX 2008, EN205626. Purdue subsequently submitted a proposed declaration prefaced [*36] with a remarks section written by Harold Steinberg, Purdue's outside patent prosecuting attorney for the '331 patent, who wrote that "as was pointed out to the Examiner at the conference, it is totally impossible to predict what dissolution rates for any particular drug will give rise to an extended duration of action." DX 2008, EN205630. In the declaration, Dr. Kaiko stated that one skilled in the art with knowledge of the controlled release hydromorphone formulation as set forth in the '341 patent could not predict whether a controlled release oxycodone formulation having a "T[max] in 2-4 hours would also provide a duration of therapeutic effect of at least 12 hours." PTX 2008, EN205635. With respect to the '598 patent, Dr. Kaiko stated that one skilled in the art with knowledge of the "teaching of a controlled-release matrix formulation of oxycodone with accompanying in vitro dissolution data" in the '598 patent could not predict "the T[max] and the duration of effect which would be achieved with such a formulation in vivo." Id. Therefore, one skilled in the art could not combine the '341 patent and the '598 patent to make the '331 invention. Id. at EN205637. Dr. Kaiko [*37] also attached an exhibit to the declaration that, under the title "INVENTION," stated that

> [the invention] acceptably controls pain over a substantially narrower, approximately four-fold (10 to 40 mg q 12h around-the-clock dosing) in approximately 90% of patients. This is in sharp contrast to the approximately eight-fold range required for approximately 90% of patients for opioid analgesics in general .... Regardless of the fact that both controlled-release oxycodone and control release morphine administered q12h around-the-clock possess qualitatively comparable clinical pharmacokinetic characteristics, [the invention] can be used over approximately 1/2 the dosage range as MS Contin [a morphine-based

> opioid drug for pain relief also manufactured by Purdue] to control 90% of patients with significant pain.

Id. at EN205639-41.

In sum, Purdue responded to the PTO's initial rejection by distinguishing the '331 invention from prior art by noting its particular analgesic effect over a four-fold dosage range, and after another rejection, subsequently distinguished it again by stating that (1) one skilled in the art could not simply replace hydromorphone with oxycodone, [*38] (2) that in vitro controlled release oxycodone formulation data did not provide a predictable correlation to in vivo data and (3) repeated the distinction raised in response to the earlier rejection, namely that the invention -in contrast to prior art - acceptably controlled pain over a four-fold dosage range for most patients.

With respect to the *'912 patent*, the PTO rejected certain claims pursuant to *28 U.S.C. § 102(b)* as being anticipated by the '341 patent because the '341 patent "teaches opioid analgesics with the claimed rate of release." DX 2033, P 000170. Purdue responded to the rejection with an "Amendment" that stated, in a section titled "The Invention," that

> Applicants have surprisingly found that even in the case of controlled-release opioid formulations having a similar in-vitro release profile, a much wider range of dosage of drug must be administered to the patient in order to achieve a satisfactory analgesic response over the requisite period of time. This is set forth, e.g., in the Specification at page 6, line 30, through page 7, line 3.

DX 2033, P 000177-78 - Amendment, dated February 22, 1995 (the "Amendment").

The referenced [*39] portion of the specification states, in part, that "the oxycodone formulations of the presently claimed invention can be used over approximately 1/2 the dosage range as compared with commercially available controlled release morphine formulations [previously set forth in the specification as an eight-fold range] to control 90% of patients with significant pain." DX 2033, P 000106-107. In the following section of the Amendment, titled "The Rejection under *35 U.S.C. § 102(b)*," Purdue continued to respond to the patent examiner's rejection by stating that one of ordinary skill in the art could not have predicted from the disclosure of the '341 patent concerning hydromorphone formulations that oxycodone - a different opioid - would have the particular plasma concentration profile set forth in the *'912 patent*, and that "in view of the '341 patent's lack of disclosure concerning oxycodone and further in view of the lack of predictability among opioid analgesics, it is respectfully requested that the Examiner reconsider and remove the rejection under *35 U.S.C. § 102(b)*." See DX 2033, P 000178, P 000181.

With respect to the *'042 patent*, [*40] the patent examiner initially rejected the claims pursuant to *35 U.S.C. § 112* due, in part, to deficiencies in the specification. DX 2009, EN205729-30. After an interview between Purdue and the examiner, Purdue deleted the term "substantially" from the claims "to bring into condition for allowance." Id. at EN205733. Subsequently, the PTO issued a Statement of Reasons for Allowance for the *'042 patent* claims that stated that "none of the references of record singly anticipate or in combination motivate one with ordinary skill in the art to formulate the particular method for reducing the dosage of oxycodone as set forth in the claims." DX 2009, EN 205735. As explicitly and definitively stated by the examiner, the *'042 patent* claims were allowed because the invention - in contrast to prior art -set forth a method for reducing dosage ranges for oxycodone. [5]

> 5 Neither party cites to the patent prosecution history of the '295 in support of their respective claim construction contentions.

[*41] Reviewing the prosecution history of the '331, '912 and *'042 patents*, this Court finds that Purdue clearly and deliberately distinguished the claimed invention over the prior art by "indicating what the claims do not cover" - specifically, controlled release oxycodone formulations that do not control pain over a four-fold dosage range for most patients. See *Spectrum, 164 F.3d at 1378-79* ("by distinguishing the claimed invention over the prior art, an applicant is indicating what the claims do not cover") (quoting *Ekchian v. Home Depot, Inc., 104 F.3d 1299,1304 (Fed. Cir. 1997)*); *Hockerson-Halberstadt, 222 F.3d at 956* ("The inventor then distinguished the prior art by arguing that the claimed invention "provides a much narrower groove for a totally different purpose .... Flowing from this statement is the inventor's clear disavowal of footwear having a groove width greater than that disclosed in the prior art"); *Lemelson v. General Mills, Inc., 968 F.2d 1202, 1206 (Fed. Cir. 1992)* ("Prosecution history is especially important when the invention involves a crowded art field, or when there is particular prior art that [*42] the applicant is trying to distinguish.").

During the prosecution history of both the '331 and *'912 patents*, Purdue distinguished the invention on additional grounds other than just reduced dosage range. However, that Purdue set forth alternative grounds for

the PTO to admit the claims does not mean that it disclaimed its earlier explicit distinction of the invention from prior art based on its reduced dosage range, especially given that it continued to assert the reduced dosage range as a reason for allowing the claims. See *Hockerson-Halberstadt, 222 F.3d at 957* (citing *Elkay Mfg. Co. v. Ebco Mfg. Co., 192 F.3d 973, 979 (Fed. Cir. 1999)* ("it is the totality of the prosecution history that must be assessed, not the individual segments of the presentation made to the Patent and Trademark Office by the applicant"); *Ekchian, 104 F.3d at 1303-04* (absent an indication by the examiner to the contrary, an examiner will consider all parts of the prosecution history); *Standard Oil Co. v. American Cyanamid Co., 774 F.2d 448, 452 (Fed. Cir. 1985)*.

As well, that the PTO rejected Purdue's initial attempt to distinguish the '331 [*43] invention on the basis of reduced dosage range does not render the distinction invalid or irrelevant. See *Springs Window Fashions LP v. Novo Indus., L.P., 323 F.3d 989, 996 (Fed. Cir. 2003)* (citing *Laitram Corp. v. Morehouse Indus., Inc., 143 F.3d 1456, 1462 (Fed. Cir. 1998)* ("The fact that an examiner placed no reliance on an applicant's statement distinguishing prior art does not mean that the statement is inconsequential for purposes of claim construction."). This Court will not "erase from the prosecution history" Purdue's clear and deliberate disavowal of controlled release oxycodone formulations that do not control pain over an approximately four-fold dosage range for approximately 90% of patients. *Hockerson-Halberstadt, 222 F.3d at 957* ("Such an argument is inimical to the public notice function provided by the prosecution history. The prosecution history constitutes a public record of the patentee's representations concerning the scope and meaning of the claims, and competitors are entitled to rely on those representations when ascertaining the degree of lawful conduct.").

Accordingly, this Court finds that Purdue deliberately [*44] and clearly relinquished, disclaimed and surrendered controlled release oxycodone formulations that do not control pain relief in approximately 90% of patients with an approximately four-fold dosage range. See *Ballard, 268 F.3d at 1359*. However, Purdue's contention to the PTO that the patents eased titration - which, as discussed previously, is the method by which dosages are adjusted in order to provide acceptable pain control without unacceptable side effects - is not a claim limitation. Any ease of titration is due, in part, to the reduced dosage range and is a benefit of the invention rather than a structural feature of the claims.

Moreover, it would be a rather strained claim construction that would result in construing the term "controlled release" with a plain and ordinary meaning - the release of an active ingredient in a controlled manner over an extended period of time - to require reduced dosage range and ease of titration. It is the invention itself, the "controlled release oxycodone formulation," that Purdue claims will control pain relief in approximately 90% of patients with an approximately four-fold dosage range. Accordingly, this Court will construe [*45] the terms "controlled release oxycodone formulation" and "controlled release dosage formulation" to require controlling pain relief in 90% of patients with a four-fold dosage range.

As it is clear from the intrinsic evidence that Purdue deliberately and with clarity limited the scope of its invention, this Court will not address the generally unpersuasive extrinsic evidence both parties have presented in support of their respective claim constructions of the term "controlled release." [6]

6 In Boehringer, this Court found, in the context of determining whether to grant a motion for a preliminary injunction, that the preambles to the '042 and '295 claims that refer to a reduction in the range of daily dosages were "not structural feature[s] of the administration of the oxycodone formulations set forth but rather simply [] a benefit of the administration of those formulations." *Boehringer, 98 F. Supp. 2d at 377*. Not only was this conclusion made, as noted, in the context of a preliminary injunction hearing, but also without analysis of the patent prosecution histories. Here, unlike in *Boehringer,* the Court is able to "construe the asserted claims based upon a final and complete record in the case." *CVI/Beta Ventures, Inc. v. Tura LP, 112 F.3d 1146, 1160 (Fed. Cir. 1997)*.

[*46] c. OxyContin controls pain relief in approximately 90% of patients over an approximate four-fold dosage range

Purdue contends that, if the Court were to construe the patent claims as requiring proof of a reduction in the range of doses, it has done so, based on (1) the testimony of Dr. Richard Payne, an attending neurologist and chief of the pain and palliative care practice at Memorial Sloan-Kettering Cancer Center, as well as President of the American Pain Society, an organization dedicated to the research and treatment of pain, and (2) OxyContin usage data as reported by the IMS National Disease and Therapeutic Index ("NDTI") and analyzed by Dr. Stanski. Endo contends that OxyContin does not control pain relief in approximately 90% of patients over an approximate four-fold dosage range, based in part on the opinion of its own expert doctor, Dr. Barbara Coda, a practicing anesthesiologist. Endo also challenges the veracity of the NDTI survey and questions whether Dr. Stanski is an

expert in the field of pharmacology such that he can assert an opinion with respect to the NDTI data.

With respect to the battling testifying experts, Dr. Payne and Dr. Coda, this Court finds that [*47] their testimony, and the related expert reports submitted by both parties, do not establish whether or not OxyContin controls pain for most patients over a four-fold dosage range. Dr. Payne testified that, based on his clinical experience, "I and most doctors are able to get the patient to a dose of OxyContin that will control their pain that ends up to be over a much narrower range of doses than would be the case with MS Contin." Tr. 99. In contrast, Dr. Coda, who admitted that she does not have "much of a pain practice" and, in contrast to Dr. Payne, has not prescribed opioids in the past three years since joining a clinical anesthesia practice, Tr. 1268, 1269, testified that a doctor's "clinical impression" is not a substitute for "scientific evidence." Tr. 1239. Dr. Coda also testified that several of Purdue's clinical studies of OxyContin - including the Heiskanen-Kalso study and the Mucci-LoRusso study - show that OxyContin does not have a four-fold dosage range. Tr. 1252, 1260. However, neither study treated patients with a 10 mg dose, twice daily, which is within the invention's claimed dosage range of 10 - 40 mg, DX 2844, DX 4145; accordingly, it is not clear to the Court [*48] what dosage range conclusions can be drawn from these studies. Each testifying expert also submitted expert reports supporting his or her opinions, as did several other experts from both sides. This Court finds that Dr. Payne's testimony is more persuasive than Dr. Coda's, but the only conclusion that can be reasonably drawn from this finding is that OxyContin controls pain over a narrower dosage range than MS Contin, but not that it controls pain over an approximately four-fold dosage range for 90% of patients.

This Court finds the NDTI data more insightful in supporting the patents' claims. Prior to trial, Endo filed a motion to exclude testimony from Dr. Stanski and Dr. Payne as related to the NDTI data because, among other reasons, the data was allegedly unreliable. This Court denied that motion, noting that Endo's argument was more relevant to a jury case as opposed to a bench trial. Tr. 11; see also *Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 596, 113 S. Ct. 2786, 125 L. Ed. 2d 469 (1993)* ("vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of [*49] attacking shaky but admissible evidence"). That "vigorous cross-examination" having now taken place, this Court finds the NDTI survey - which Endo admits is itself methodologically and statistically sound [7] - and Dr. Payne's testimony proves by a preponderance of the evidence that OxyContin provides adequate pain relief for approximately 90% of patients over an approximate four-fold dosage range.

7 See Endo's Memorandum In Support of its Motion In Limine to Exclude the Testimony of Purdue's Experts, Donald R. Stanski, M.D. and Richard Payne, M.D., to the Extent it is Based on NDTI Data, Related Materials and/or the "Meta Study" at 8; see also Tr. 1531 (testimony of Dr. Paul Willis Allen, Endo's expert and a former marketing executive at IMS Health).

As an initial matter, this Court finds that Dr. Stanski, a professor of anesthesia at Stanford University and former chair of the anesthesia department who has published over ninety articles in the area of anesthetic and analgesic drugs, who has been involved [*50] in the development of opioid analgesics for most of his 29 year career in anesthesiology, and who has used NDTI data in his consulting career to understand dosing patterns, is qualified to testify as an expert in the field of pharmacology such that he can assert an opinion with respect to the NDTI data. Tr. 631-33, 804. The NDTI survey "provides statistical information about the patterns and treatment of disease encountered in office-based practice in the continental United States," from a monthly sample of 2200 physicians who specialize in diagnosing and treating disease, which is then extrapolated to reflect approximately 85% of office-based physicians. PTX 842, 28-2. The IMS Health Information Services Manual acknowledges that NDTI survey data does not cover a majority of the physicians in America, but it claims that most of the doctors not covered are specialists that only see patients after they have seen doctors who are covered by the NDTI survey. PTX 842, 28-4. The NDTI survey forms provide space for doctors to record the specific product and exact dosage they issued or recommended to their patients, as well as a separate space to indicate whether the product was actually issued [*51] or whether it was only recommended. PTX 842, 28-12.

Surveying the "uses" of OxyContin reported by NDTI between 1996-2001 - "uses" consisting of 85-90% prescriptions [8] - Dr. Stanski concluded that 84.4% of the 6,000,000 uses fall with the four-fold range disclosed in the patents in suit (20 mg - 80 mg/day for twice per day usage). See Tr. 814; PTX 578. As Endo does not challenge the methodology of the NDTI survey, and indeed cites cases supporting the use of NDTI data to compute the number of times doctors recommend a particular drug in comparison to other drugs, this Court will utilize the survey for the limited purpose of showing that it is "literally true" that there have been approximately 6,000,000 "uses" of OxyContin between 1996-2001 and, of those 6,000,000 "uses," approximately 84% have fallen within the four-fold range of the claims. See, e.g.,

Bristol-Myers Co. v. F.T.C., 738 F.2d 554, 563 (2d Cir. 1984) (relying on NDTI survey to conclude that physicians recommended a drug more often than three competing products); *McNeilab, Inc. v American Home Products Corp., 501 F. Supp. 517, 524 (S.D.N.Y. 1980)* (citing NDTI data showing that it [*52] was "literally true" that one drug was recommended to patients more than another drug).

8 Dr. Stanski testified that "uses" is a "prescribing event" when a doctor prescribed specific drugs at specific dosage strengths to a patient. Tr. 712, 716. Dr. Allen defined "uses" more broadly to include events where a doctor, in filling out the NDTI survey, recalled the product that was appropriate for a patient's diagnosis. Tr. 1537. Although Dr. Allen testified that NDTI data is not prescription data, Tr. 1524, he never addressed whether or not 85-90% of the data is, in fact, prescription data. Tr. 814.

Given that OxyContin is an analgesic and, as set forth in the testimony of Dr. Payne, an effective analgesic, Tr. 94, 107-09, this Court assumes that "uses," and correspondingly, prescriptions written by doctors, provide an indication that the patient's pain is being adequately relieved by OxyContin, although it notes that both Dr. Coda and Dr. Payne testified that the NDTI data does not, by itself, indicate whether [*53] or not patients were "adequately medicated." See Tr. 145-46; Tr. 1243-46, 1292. Endo has not presented any evidence that OxyContin is not an effective analgesic, and it would appear incongruous for Endo to file an ANDA seeking approval to manufacture and sell a bioequivalent version of an analgesic that failed to adequately control pain. This Court is not using NDTI as evidence to support the conclusion (1) that OxyContin is more easily titratable than other opioid drugs or (2) even that its dosage range for adequate pain relief for most patients is twice as narrow as for MS Contin or other drugs for pain relief.

Dr. Stanski admitted that (1) he had not seen NDTI data used in any "peer-reviewed publications," Tr. 805, even though the IMS Health Information Services Manual asserts that its NDTI data was used in an article in the Journal of the American Medical Association, PTX 842, 28-3, (2) that certain portions of the data were eliminated prior to computation, including 1/2 tablet recommendations and one time per day uses, Tr. 811 - neither of which are uses contemplated anywhere in the claims, specifications or prosecution histories of the patents, (3) that he did not analyze [*54] the data for sampling error, Tr. 814-15, and (4) he, in fact, testified that the NDTI data was "a very important marketing tool," Tr. 804. Dr. Coda also noted a number of drawbacks to using NDTI data. Tr. 1242-43. However, this Court is only utilizing the methodologically sound NDTI data for the limited purpose of quantifying the number of "uses" and corresponding prescribed dosages.

Accordingly, Purdue has proven that the patents in suit adequately control pain for approximately 90% of patients within a four-fold dosage range.

2. Comparison of Endo's proposed ANDA formulation to Purdue's OxyContin

To establish infringement, Purdue must show by a preponderance of the evidence that the accused device contains, either literally or by equivalents, the limitations of the claimed invention. See *Bayer AG v. Elan Pharm. Research Corp., 212 F.3d 1241, 1247 (Fed. Cir. 2000)* (citation omitted); *Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc., 98 F.3d 1563, 1574 (Fed. Cir. 1996)*. Pursuant to a finding of literal infringement, the patentee must establish that every limitation set forth in the properly construed claim reads on, or in [*55] other words is found in, the accused product, exactly. *Allen Engineering Corp. v. Bartell Indus. Inc., 299 F.3d 1336, 1345 (Fed. Cir. 2002)*. If any claim limitation is absent from the accused product, there is no literal infringement as a matter of law. See *Bayer AG, 212 F.3d at 1247*.

Endo does not dispute that its proposed drug, filed pursuant to an ANDA, is bioequivalent to OxyContin, for the 10 mg, 20 mg, 40 mg and 80 mg tablets, as it must be in order to secure approval from the FDA. See *21 U.S.C. § 355(j)(2)(A)*; PTX 845A, 846A, 847A, Endo provided the FDA with one steady state pharmacokinetic study for its 40 mg ANDA formulation that reported C[max], T[max], C[min] and T[min] within the ranges set forth in the patent claims. PTX 845A. Specifically, Endo recorded C[max] as 36.73 ng/ml, C[min] as 17.91 ng/ml, T[max] as 3 hrs and T[min] measured at "just prior to dose administration" which, for steady state testing of 12 hour formulations, occurred at 12 hours. PTX 845A, EN003395, EN003397, EN003412; PTX 845, EN003410. These numbers fall within the ranges set forth in the claims of the patents in suit. [*56] For example, claim 1 of the '912 and *'042 patent*, and Claim 2 of the *'295 patent* provide for a C[max] of between 6 to 60 ng/ml, a C[min] between 3 to 120 ng/ml, a T[max] of 2-4 hours and a T[min] of 10 to 14 hours. Applying the concept of linear kinetics, where a doubling of the dose results in a doubling of the blood plasma concentration, which experts from both Endo and Purdue accept as a viable method of determining blood plasma concentration, Tr. 1156, Tr. 691-92, Endo's 10 mg, 20 mg and 80 mg proposed drugs also infringe the pharmacokinetic claims of the patents in suit. See PTX 422, EN206132, EN206190; Claim 2 of the '912 and *'042 patents*; Claim 1 of the *'295 patent*.

Endo's proposed ANDA formulations also infringe the composition claims as well. Endo does not dispute that the formulations for the 10, 20, 40 and 80 mg proposed ANDA formulations all contain between 10 and 160 mg of oxycodone hydrochloride (an oxycodone salt), Eudragit, a release controlling agent that is an acrylic resin and consists of hydrophilic polymers and Avicel, a diluent that is listed in the ANDA application as a "filler." PTX 845A, EN003903; PTX 846A, EN052849-50; PTX 847A, EN052849; Tr. [*57] 1416. Compare this composition with the composition of Claim 3 of the *'912 patent* and Claims 4, 6 and 7 of the *'295 patent*: "oxycodone or a salt thereof in an amount from about 10 to about 160 mg," "a controlled release matrix selected from the group consisting of hydrophilic polymers ...," and " a suitable amount of pharmaceutical diluent." Claim 4 of the *'912 patent* states that the controlled release matrix of Claim 3 "comprises an acrylic resin." While there are distinctions in the composition of the parties' respective controlled release matrixes -- Dr. Danny Kao, employed at Endo as its principal scientific advisor, testified that Endo's controlled release matrix contains only Eudragit while Purdue's matrix contains Eudragit and stearyl alcohol - among other differences, Tr. 1449-54, the claims are worded broadly enough to encompass these differences, and the specifications and prosecution histories do not otherwise limit the composition claims. Accordingly, Endo's proposed ANDA formulation literally infringes the composition claims of the patents in suit.

Endo contends that since the patients in its 40 mg ANDA formulation steady state pharmacokinetic study took a dose of naltrexone [*58] prior to their morning doses, and naltrexone quantitatively alters the rate and extent of absorption of opioids into humans, the resultant pharmacokinetics will be altered. Since the asserted claims of the patents in suit make no reference to naltrexone, Endo contends there is no reliable evidence that its ANDA formulation falls within the patents' pharmacokinetic claims. Naltrexone is an opioid antagonist that "prevents an opioid from creating any pharmacological effect on the subject" and is used to protect patients "from the narcotic effects" of oxycodone that could occur at high doses. Tr. 702; PTX 845A, EN003397. Subjects in Endo's study - who were "normal, healthy male volunteers," PTX 845A, EN003397, - were given naltrexone "to prevent cardiovascular and gastrointestinal adverse effects associated with the administration of oxycodone to opiate-naive subjects." Id. at EN003413, EN003397. [9]

9 The excipients listed on Endo's proposed physician inserts for its ANDA formulation do not include naltrexone, PTX 422, EN206125. Naltrexone was also listed as and administered as a separate tablet in Endo's study. Id. at EN003404. The title of the study itself is the "Steady-State Bioequivalence of [Endo's 40 mg proposed ANDA formulation]," not the "Steady-State Bioequivalence of [Endo's 40 mg proposed ANDA formulation and separate 50 mg naltrexone tablet]."

[*59] Although Endo has asserted that naltrexone would alter the pharmacokinetics of a controlled release oxycodone formulation, Endo does not cite any scientific articles or provide any expert testimony that directly supports this hypothesis and the Court is thus unable to adopt Endo's assertion as fact. On this basis alone, this Court could determine that Endo infringes the pharmacokinetic claims of the patents in suit. In the single published article cited by Endo, the authors reported that in the presence of naltrexone, the C[max] for controlled release *morphine* was 14% higher than the corresponding value without naltrexone and the T[max] was 23% lower, but that the difference for T[max] could not be considered statistically significant because of the large variation in T[max] measurements. DX 2145; Tr. 703-05.

For purposes of analysis, this Court assumes, without deciding, that naltrexone would have the same impact on controlled release oxycodone formulations as it did on the controlled release morphine formulation used in the article. The article does not posit such a replacement, but Dr. Michael Mayersohn, Endo's pharmaceutics expert, testified that, pursuant to an obviousness [*60] analysis, one skilled in the art could replace an opioid with another opioid and yield predictable blood plasma concentration results. Tr. 1128. If the pharmacokinetic properties of Endo's ANDA formulation were adjusted due to the presence of naltrexone pursuant to the percentages set forth in the article, the revised C[max] would be 41.87 ng/ml and T[max] would be 2.31 hours, which are still well within the range of the claims of the patents in suit. See, e.g., Claims 1 of the *'042 Patent* and *'912 Patent* and Claim 2 of the *'295 Patent* (providing for a range of C[max] values from 6to60 ng/ml and T[max] values from 2 to 4.5 hours); Tr. 705-06.

Accordingly, Endo's ANDA formulation infringes the claims of the patents in suit, including the limitation that the patent claims must control pain relief in approximately 90% of patients over a four-fold range of dosages. Although Purdue failed to perform a clinical analysis of the efficacy of a four-fold dosage range of Endo's proposed ANDA formulation, Endo cannot avoid a finding of infringement. This Court credits the testimony of Dr. Stanski who, after reviewing the proposed package insert Endo submitted to the FDA, testified [*61] that "Endo's [proposed ANDA formulation] will result in a reduced range of dosage because of the bioequivalence that has been demonstrated by Endo." Tr.

718, 834-37; PTX 422. In addition, Dr. Mayersohn - Endo's expert - testified that in vitro release profiles (charts showing the percentage of an active ingredient dissolved in the laboratory over time) are predictive of in vivo profiles (charts showing the blood plasma concentration of an active ingredient in the human body over time), Tr. 1128, 1140-42, and that in vivo profiles of controlled release hydromorphone formulations are predictive of the in vivo profiles of controlled release oxycodone formulations, Tr. 1132-36. See also Dr. Mayersohn's Expert Reports. Accordingly, though not specifically addressed by Endo, this Court can see no reason why these predictive qualities cannot extend to predicting dosage ranges of bioequivalent formulations. That Endo's ANDA formulation is bioequivalent to OxyContin does not by itself result in infringement, see *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc., 288 F. Supp. 2d 562, 2003 U.S. Dist. LEXIS 19105, 2003 WL 22434211 (S.D.N.Y. 2003)*, but bioequivalence is relevant to infringement [*62] here, where pharmacokinetic properties are included as limitations to the claims at issue in the patents in suit. As Purdue has already proven by a preponderance of the evidence that OxyContin controls pain in most patients over a four-fold dosage range, and OxyContin and Endo's ANDA formulation are bioequivalent, and Endo's ANDA formulation infringes the composition and pharmacokinetic claims of the patents in suit, Purdue has proven by a preponderance of the evidence that Endo infringed its patents in suit.

B. Inequitable Conduct

An otherwise valid patent may be rendered unenforceable by virtue of inequitable conduct committed during the prosecution of the patent application before the Patent Office. Patent applicants are required to prosecute patent applications "with candor, good faith, and honesty." *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc., 326 F.3d 1226, 1233 (Fed. Cir. 2003)* (quoting *Molins PLC v. Textron, Inc., 48 F.3d 1172, 1178 (Fed. Cir. 1995))*. "A breach of this duty, when coupled with an intent to deceive or mislead the PTO, constitutes inequitable conduct, which, when proven, renders the patent unenforceable." Id. [*63]

"Inequitable conduct entails a two-step analysis: first, a determination of whether the withheld reference meets the threshold level of materiality and intent to mislead, and second, a weighing of the materiality and intent 'in light of all the circumstances' to determine 'whether the applicant's conduct is so culpable that the patent should be held unenforceable.'" *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH, 237 F.3d 1359, 1366* (quoting *Baxter Int'l, Inc. v. McGraw, Inc., 149 F.3d 1321, 1327 (Fed. Cir. 1998))*. "Inequitable conduct includes affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive." See *CFMT, Inc. v. CFM Tech., Inc., 349 F.3d 1333, 1340 (Fed. Cir. 2003)* (quoting *Molins PLC v. Textron, Inc., 48 F.3d 1172, 1178 (Fed. Cir. 1995))*. "When balanced against high materiality, the showing of intent can be proportionally less." *Rhone-Poulenc Roher, 326 F.3d at 1233* (citing *Brasseler, U.S.A.I., L.P. v. Stryker Sales Corp., 267 F.3d 1370, 1381 (Fed. Cir. 2001))*.

Since a patent is presumed valid, [*64] see *35 U.S.C. § 282*, Endo must show by "clear and convincing evidence" that Purdue failed to disclose material information with an intent to mislead the PTO. *CFMT, 349 F.3d at 1340*. "The 'clear and convincing' standard of proof of facts is an intermediate standard which lies somewhere between 'beyond a reasonable doubt' and 'preponderance of the evidence.'" *Buildex, Inc. v. Kason Indus., Inc., 849 F.2d 1461, 1463 (Fed. Cir. 1988)* (quotation omitted). "Although not susceptible to precise definition, 'clear and convincing' evidence has been described as evidence which produces in the mind of the trier of fact 'an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" Id. (quotation omitted).

There are two interpretations of materiality that courts have relied upon in evaluating a claim of inequitable conduct. Prior to March 16, 1992, the Federal Circuit "held that materiality for purposes of an inequitable conduct determination required a showing that 'a reasonable examiner would have considered such prior art important in deciding whether to allow the parent application.'" *Dayco Products, Inc. v. Total Containment, Inc., 329 F.3d 1358, 1363 (Fed. Cir. 2003)*. [*65] "Information did not need to be prior art in order to be material, but 'instead embrace[d] any information that a reasonable examiner would substantially likely consider important in deciding whether to allow an application to issue as a patent.'" Id. (quoting *Akron Polymer Container Corp. v. Exxel Container, Inc., 148 F.3d 1380, 1382 (Fed. Cir. 1998))*. However, in March 1992, the PTO amended its rules to provide for a definition of materiality that was supposedly "clearer and more objective." *Duty of Disclosure, 57 Fed. Reg. 2021, 2024 (January 17, 1992)*. "The new rule reiterated the preexisting 'duty of candor and good faith,' but more narrowly defined materiality, providing for disclosure where the information establishes either 'a prima facie case of unpatentability' or 'refutes, or is inconsistent with a position the applicant takes.'" *Dayco Products, 329 F.3d at 1363-64*. [10] Since the 1992 amendment, the Federal Circuit has continued to apply the reasonable examiner standard to cases that were prosecuted under the earlier version of *37 C.F.R. § 1.56(b)* but has "not decided whether the standard for

materiality [*66] in inequitable conduct cases is governed by equitable principles or by the Patent Office's rules." *Id. at 1364.* However, "the new standard was not intended to constitute a significant substantive break with the previous standard." *Hoffmann-La Roche, Inc. v. Promega Corp., 323 F.3d 1354, 1368 n.2 (Fed. Cir. 2003).* Endo contends that Purdue committed inequitable conduct before the PTO both prior to and subsequent to March 16, 1992, so both standards should apply. Regardless of which standard is applied, Purdue misrepresented material facts to the PTO.

10 Specifically, the rule provides that:

> information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and
>
> (1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or
>
> (2) It refutes, or is inconsistent with, a position the applicant takes in:
>
> (i) Opposing an argument of unpatentability relied on by the Office, or
>
> (ii) Asserting an argument of patentability.
>
> A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.
>
> *37 C.F.R. § 1.56(b) (2003)*

[*67] A finding of intent does not require direct evidence and can be inferred from the facts of the action. See *Rhone-Poulenc Roher, 326 F.3d at 1239.* "Where withheld information is material and the patentee knew or should have known of that materiality, he or she can expect to have great difficulty in establishing subjective good faith sufficient to overcome an inference of intent to mislead." *Id. at 1240.* However, "mere gross negligence is insufficient to justify an inference of an intent to deceive" the Patent Office. *Baxter Int'l, 149 F.3d at 1329* (citing *Kingsdown Med. Consultants, Ltd. v. Hollister, Inc., 863 F.2d 867, 876 (Fed. Cir. 1988)* (en banc)). "In determining inequitable conduct, a trial court may look beyond the final claims to their antecedents," including claims of parent patents when such inequitable conduct is material to the claims of the continuation or divisional patents. *Baxter Int'l, 149 F.3d at 1332* (quoting *Fox Indus., Inc. v. Structural Pres. Sys., Inc., 922 F.2d 801, 803-04 (Fed. Cir. 1990)).*

Endo contends that Purdue committed inequitable conduct when it allegedly [*68] misrepresented the material fact that Purdue had "surprisingly discovered" that its invention reduced the dosage range and eased titration in comparison to other opioid formulations. The misrepresentation lay in intentionally failing to disclose material information inconsistent with these assertions. [11]

11 Endo also contends that Purdue misrepresented the material fact that a T[max] of 2 to 4 1/2 hours was surprising for a 12-hour controlled release opioid by failing to disclose that other opioids had the same T[max] range. Because Purdue committed inequitable conduct by misrepresenting its "surprising[] discovery" of a reduced dosage range, thus rendering the patents in suit invalid, this Court need not decide whether or not Purdue committed other acts of inequitable conduct before the PTO.

The specifications of the patents in suit repeatedly note that the inventors "surprisingly discovered" that the controlled release oxycodone formulation "acceptably control[s] pain over a substantially narrower, [*69] approximately four-fold range (10 to 40 mg every 12 hours - around-the-clock dosing) in approximately 90% of patients. This is in sharp contrast to the approximately eight-fold range required ... for opioid analgesics in general." The *'912 patent*, 3: 34-41. See also *'912 Patent*, 3:42-47; 3:67 - 4:8; 4:51-57; 1:10-45; 4:51-63. [12] As discussed previously, the prosecution histories of the patents in suit are replete with examples where Purdue asserted to the PTO that the invention provided pain relief for most patients over a four-fold dosage range, leading to easier titration. See supra pgs. 19 to 23. In fact, after reviewing the claims, specification and prosecution histories of the patents in suit, this Court construed the claim term "controlled release oxycodone formulation" to require adequate pain relief in approximately 90% of patients over an approximately four-fold dosage range, although ease of titration was not construed so as to limit the claims. See also *Boehringer, 98 F. Supp. 2d at 375* ("it was a principal purpose of the invention to facilitate the titration process by reducing the range of daily dosages needed to provide effective pain relief [*70] across the spectrum of patients").

12 As noted supra pg. 11, the specifications of the '912, '042 and *'295 patents* are identical.

However, during the bench trial, Dr. Kaiko admitted that he had "no scientific proof" at the time of filing the

'912 patent that the inventions of the patents exhibited a reduced dosage range. Tr. 407. Instead of scientific proof, Dr. Kaiko testified that he had an "insight ... that the range around the oral bioavailability of oxycodone had to be narrower than the range around the oral bioavailability of morphine." Tr. 172. With this "insight," he "envisioned [a] ... proposed controlled-release oxycodone product ... having an approximate four-fold range." Tr. 176.

To support this insight, he reviewed and "quantitatively analyzed" the "individual patient daily dosages in patients who had been titrated with MS Contin [a morphine-based pain relief drug]" in order to determine that there was an eight-fold range of dosages for morphine, Tr. 173. Dr. Kaiko determined that controlled [*71] release oxycodone had a four-fold range of dosages --in contrast to the eight-fold range of dosages for controlled release morphine -- due to certain factors he knew about oxycodone, including its known oral bioavailability, its effectiveness, its short elimination half-life and "this profile of blood levels that I had in mind." Tr. 176. Dr. Kaiko also provided a demonstrative exhibit that purported to demonstrate his analysis of the morphine data combined with his insights into oxycodone. DX 1061. Purdue failed to provide to the Court any documentary evidence of any actual "individual patient daily dosages" or any other documents that Dr. Kaiko reviewed in coming up with his "insight." Dr. Kaiko in fact testified that no documents exist that show his analysis of data displayed as demonstrative exhibit DX 1061, and that no data at all existed for his insight that a controlled release oxycodone formulation would have 1/2 the dosage range of morphine. Tr. 405-07.

Purdue does not dispute that no clinical studies existed - at either the time of filing or immediately subsequent to the allowance of the claims of the patents in suit - to support the patents' disclosure of a four-fold range [*72] of doses that treat approximately 90% of patients. See Purdue's Opening Brief After Trial at 48. In fact, the evidence Purdue used at trial to prove the patents' reduction in dosage ranges consisted of NDTI data from 1996 to 2001, well after the filing dates of all the '912 and *'042 patents*, and covering only three months worth of data prior to the March 19, 1996 filing of the *'295 patent*. See PTX 578; PTX 7-9. Instead, Purdue contends that the word "discovery" can include purely mental acts so Dr. Kaiko had in fact "discovered" a reduction in dosage ranges. Harold Steinberg, Esq., a patent attorney who prosecuted and supervised the prosecution of the '331 patent and a partner in the firm Steinberg, Raskin & Davidson that prosecuted the patents in suit, described such discoveries as "made in the mind, not necessarily in the laboratory. I can give you a good example. Einstein's E = mc<2>. Nothing in the laboratory for it, but the discovery was made in his mind." Tr. 1620. Purdue also cites a dictionary definition of the related term "discover" as meaning "to make known or to obtain knowledge of for the first time." Merriam-Webster New Ninth Collegiate Dictionary 361 (9th [*73] ed. 1989). Accordingly, Purdue contends that it did not need to produce any evidence to the PTO beyond the declaration from Dr. Kaiko stating that he had "surprisingly discovered" this result because the declaration was factual evidence that supported this statement. See also *CFMT, 349 F.3d at 1342* (To support an "unexpected result," a patent applicant may, during prosecution of the patent before the PTO, "submit objective factual evidence to the PTO in the form of patents, technical literature, and declarations under *37 C.F.R. § 1.132 (2003)*.").

In contrast, Endo's expert, Gerald Bjorge, Esq., a former examiner and Administrative Patent Judge at the PTO, testified that, pursuant to the Manual of Patent Examining Procedure, an "insight or theory should be described in the present tense or in language like 'can be done,' 'could be done,' something that imports the notion to the reader, to the scientific community, the public at large and particularly the examiner that something has not yet been actually done or actually reduced to practice." Tr. 1560; see also Manual of Patent Examining Procedure ("MPEP") § 2004.8 (8th ed. 2003) ("Stating [*74] that an experiment 'was run' or 'was conducted' when in fact the experiment was not run or conducted is a misrepresentation of the facts."). [13]

13 In addition, Mr. Steinberg testified that the support given to the PTO for "unexpected results" should be "proof by comparative tests." Tr. 1628. See also DX 2008, EN205626.

This Court finds, by clear and convincing evidence that a reasonable examiner would have considered important the fact that Purdue did not have any "scientific proof" that the claimed invention actually provided adequate pain relief for most people over a four-fold dosage range to be important information: and that the lack of that proof is inconsistent with Purdue's reduced dosage assertion. Although the term "discovery" has a broad dictionary definition that can theoretically cover mere "insights," Purdue repeatedly and convincingly stated to the PTO that it had discovered an oxycodone formulation that did not simply control pain over a reduced dosage range, but controlled pain over a "four-fold" [*75] range of doses for "approximately 90%" of patients. Purdue asserted to the PTO that this "result" [14] was of "extreme clinical importance." DX 2033, P 000177 ("The above result [that the oxycodone formulations claimed can be used over approximately 1/2 the dosage range as morphine] is surprising and of extreme clinical importance"); DX 2008, EN205621 ("One skilled in the art would cer-

tainly not arrive at this surprising result without the benefit of hindsight."). Such definitive statements to the PTO would clearly be undercut if the PTO were aware that the statements lacked any support other than Dr. Kaiko's assertions and "insight."

> 14 See Webster's Third New International Dictionary 1937 (1993) (defining a "result" as "something obtained, achieved, or brought about by calculation, investigation, or similar activity (as an answer to a problem or knowledge gained by scientific inquiry)"). The Federal Circuit has used Webster's Third New International Dictionary to help construe claims. See *Omega, 334 F.3d at 1322*.

[*76] Clearly, the assertion of reduced dosage ranges is itself material - indeed, it is even a claim limitation. Even if this Court did not so limit the claims, these statements would still be material, since as previously discussed, the patent examiner considered these statements decisive in allowing the *'042 patent* application to issue. See *Hoffman-La Rouche, 323 F.3d at 1367* (citing *PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc., 225 F.3d 1315, 1322 (Fed. Cir. 2000)*; see, e.g., DX 2009, EN 205735 - Statement of Reasons for Allowance of the *'042 patent* ("none of the references of record singly anticipate or in combination motivate one with ordinary skill in the art to formulate the particular method for reducing the dosage of oxycodone as set forth in the claims"). Consequently, information inconsistent with the position that Purdue took before the PTO that the invention controlled pain for most patients over a four-fold dosage range - including information that the position was just an "insight" that was not supported by any "scientific proof" -- is material. See C.F.R. *§ 1.56(b)*.

The Federal Circuit recently affirmed a district court's [*77] finding of misrepresentation in similar circumstances. In Hoffmann-La Roche, the Federal Circuit found that a patentee misrepresented the fact that an example - described in the specification in the past tense and including results - had not actually been performed. *323 F.3d at 1364-66*. Although here, in contrast to *Hoffman-La Roche,* neither the patents in suit themselves nor their prosecution histories describe the process by which Purdue discovered that a four-fold dosage range would adequately relieve pain in 90% of patients, the fact that Purdue (1) described the surprising discovery (the "result") in concise, quantified terms, (2) described it as having occurred in the past tense, (3) considered the discovery "absolutely critical to the invention," Tr. 172, and most importantly (4) used this precisely quantified "discovery" throughout the prosecution of the '331, '912 and *'042 patents* as a prominent, and at times, the only, argument in favor of patentability before the PTO, resulting in allowance of the claims, support this Court's finding that Purdue misrepresented a material fact. *Id. at 1368* ("a reasonable examiner would have wanted to [*78] know that the patentability argument ... was unsupported by the experimental results cited by the inventors"); *Grefco, Inc., v. Kewanee Indus., Inc., 499 F. Supp. 844, 865-70 (D. Del. 1980)*. See also *CFMT, 349 F.3d at 1341-1342* (asserted "unexpected results" determined not to be material misrepresentations where the statements were in fact accurate and "natural, expected results" that the examiner did not rely on in allowing the application); MPEP § 2004.8.

We now turn to the question of intent. As noted previously, "when balanced against high materiality, the showing of intent can be proportionally less." *Rhone-Poulenc Roher, 326 F.3d at 1233*. "Proof of high materiality and that the applicant knew or should have known of that materiality makes it difficult to show good faith to overcome an inference of intent to mislead." *Semiconductor Energy Lab. Co. v. Samsung Elecs. Co., 204 F.3d 1368, 1375 (Fed Cir. 2000)*; *Critikon, Inc. v. Becton Dickinson Vascular Access, Inc., 120 F.3d 1253, 1256 (Fed. Cir. 1997)*. "Evidence of good faith must be considered in determining whether inequitable conduct has been [*79] shown by clear and convincing evidence." See *Baxter Int'l, 149 F.3d at 1330*. See also *Ulead Systems, Inc. v. Lex Computer & Management Corp., 351 F.3d 1139, 2003 U.S. App. LEXIS 24718, 2003 WL 22889687, at *6 (Fed. Cir. Dec. 9, 2003)*.

Purdue contends that it believed in good faith that it had "discovered" that OxyContin provided pain relief over a reduced, four-fold dosage range. However, Dr. Kaiko - in addition to his testimony about discovering the reduction in dosage ranges -- testified that at no time prior, during, or subsequent to the prosecution of the patents in suit did there exist at Purdue a "set of procedures and methods" that could "provide definitive conclusions" that OxyContin was "the most easily titratable strong analgesic," and that such a test would require "hundreds of thousands of patients." Tr. 235, 246. Dr. Goldenheim - to whom Dr. Kaiko directly reported since he started working at Purdue, Tr. 969 - testified that as of October 20, 1993, Purdue's researchers "weren't anywhere close" to proving that OxyContin was "the most efficiently titratable long-acting strong analgesic," and these titration claims were "clearly Bob Kaiko's vision." Tr. 984. As discussed earlier [*80] in this Opinion, titration is the method by which dosages are adjusted in order to provide acceptable pain control without unacceptable side effects. Tr. 99, 169, 1233. Thus, a reduction in dosage ranges would directly improve titration, as Purdue itself states in the specifications of the patents in suit:

> The clinical significance provided by the controlled release oxycodone formulations of the present invention at a dosage range from about 10 to about 40 mg every 12 hours for acceptable pain management in approximately 90% of patients with moderate to severe pain, as compared to other opioid analgesics requiring approximately twice the dosage range provides for the most efficient and humane method of managing pain requiring repeated dosing. The expertise and time of physicians and nurses, as well as the duration of unacceptable pain patients must endure during the opioid analgesic titration process is substantially reduced through the efficiency of the controlled release oxycodone formulations of the present invention.

See, e.g., the '295 and *'912 patents*, Cols. 4:51-63; the *'042 Patent*, 4:53-65; see also DX 2008, EN 206520.

Dr. Goldenheim also testified [*81] that "I think that being easy to titrate would be one of the components that one would expect in a formulation whose benefit would be associated with a reduced dosage range. So if it were difficult to titrate, if it were not easy to titrate, I wouldn't expect that benefit to accrue." Tr. 990. Accordingly, Purdue's admitted inability to prove titration claims undercuts any good faith belief that the inventions provided pain relief for most patients over a reduced, four-fold dosage range.

Documents created by Purdue contemporaneous to the prosecution of the patents in suit also undercut Purdue's good faith contention. For example, a July 16, 1990 internal memo written by Dr. Kaiko stated that, with respect to any claims of reduced dosage range and resulting ease of titration, "while the theoretical argument may be relatively strong using available data, it may be difficult to demonstrate these claims within the context of efficacy studies. Thus, an acceptance of a priority program for controlled-release oxycodone should not assume that all these claims can be demonstrated." DX 3165. Just four months prior to the filing of the '331 patent, Dr. Goldenheim wrote in a memo to Dr. Kaiko [*82] and other Purdue scientists that "OxyContin *may* have advantages over MS Contin in terms of less variability in dose required." DX 3226 (italics added). In a memo with the subject line "OxyContin Advantages," dated September 28, 1993, nearly one year after Purdue first told the PTO that it had "surprisingly discovered" the inventions' reduced dosage range, Dr. Kaiko wrote that "one would expect that [oxycodone's] characteristics would translate into a number of desirable clinical outcomes such as:... the finding that a narrower range of dosages of oxycodone are required to manage a group of patients than with the utilization of drugs with a lower oral bioavailability," and requested that Purdue researchers focus on these outcomes. DX 3629. Thus, more than a year after representing to the PTO that a four-fold range of dosages was a "surprising discovery," internal memoranda reveal that Dr. Kaiko considered his "surprising discovery" only a non-quantified "expectation" that needed additional studies and supporting data. Id. Shortly thereafter, Dr. Goldenheim noted in response to a memo from Dr. Kaiko where Dr. Kaiko asserted that OxyContin was the "most efficiently titratable [*83] long-acting strong analgesic," that "this is a theory - not yet proven. we will have to see." DX 3156.

Purdue attempts to limit many of these comments as only being made in the context of Purdue's efforts to receive FDA approval for the comparative claim "most efficiently titratable strong analgesic," Tr. 982, and accordingly these comments do not address any assertions Purdue made to the PTO about the reduced dosage ranges of the patents in suit. However, as discussed above, a reduced dosage range is directly related to easier titration; any concerns about proving the latter must affect belief in the former, especially as Purdue's reduced dosage range assertion is - like the titration assertion - made in a comparative context - i.e., "other opioid analgesics require approximately twice the dosage range." '295 and *'912 patents*, Cols. 4:51-63; *'042 Patent*, 4:53-65.

Accordingly, this Court finds that any good faith belief that Purdue had "discovered" the reduction in dosage range is substantially undercut by its admitted inability to prove, or even to develop, a "set of procedures and methods" to prove this reduction in dosage range (and related case of titration), and cannot "overcome [*84] an inference of intent to mislead." *Semiconductor Energy, 204 F.3d at 1375*. In any event, good faith does not suffice to negate a finding of intent. In Hoffmann-La Roche v. Promega, the patentees made a similar argument to the Federal Circuit that "'because one cannot intentionally deceive by representing what one honestly believes, the district court's [finding that the intent element of inequitable conduct had been met] judgment cannot stand." *Hoffmann-La Roche, 323 F.3d at 1367*. In response, the Federal Circuit stated that "the inventors may indeed have believed that they had discovered a novel enzyme, but that belief does not permit them to make misrepresentations in seeking to persuade the examiner to issue a patent for that enzyme." Id. Here, even assuming Purdue believed in good faith that it had discovered a novel result - the four-fold dosage range that relieved pain in most patients -that belief did not entitle it to deceptively

withhold from the PTO the fact that it did not have any "scientific proof" to support its discovery, or even a method or procedure in place for proving its discovery. Purdue made a deliberate decision to [*85] misrepresent to the PTO a "theoretical argument" and an "expectation" as a precisely quantified "result" or "discovery." Accordingly, Endo has proven, by clear and convincing evidence, that Purdue intentionally misrepresented its "discovery" to the PTO.

This Court is aware of "the ease of opportunistic challenge to the conduct of experimental science in the patent context," and that inequitable conduct cannot be founded merely on a finding that a patentee included "predicted test results and prophetic examples" in their specification - such "paper examples" are explicitly permitted. See *Hoffmann-La Roche, 323 F.3d at 1373, 1377* (dissent, Newman, J.); MPEP § 608.01(p). However, after weighing the materiality and intent "in light of all the circumstances," this Court concludes that Purdue "is so culpable that the patent should be held unenforceable." *Boehringer, 237 F.3d at 1366* (quoting *Baxter Int'l, 149 F.3d at 1327*).

The record as a whole reflects a clear pattern of intentional misrepresentation of a material fact - Purdue knew that it did not have "scientific proof" of its "discovery," yet repeatedly asserted its "discovery" to [*86] the PTO in precise, quantified, past-tense language. And while it is true that "it is not inequitable conduct to omit telling the patent examiner information that the applicant in good faith believes is not material to patentability," see *Allied Colloids Inc. v. American Cyanamid Co., 64 F.3d 1570, 1578 (Fed. Cir. 1995)*, a patent applicant cannot "cultivate ignorance, or disregard numerous warnings that material information or prior art may exist, merely to avoid actual knowledge of that information or prior art." *FMC Corp. v. Hennessy Industries. Inc., 836 F.2d 521, 526 n.6 (Fed. Cir. 1987)*. Here, the "discovery" was so "absolutely critical" to the invention - Tr. 172 (testimony of Dr. Kaiko) - that Purdue initially cited the discovery as the sole reason why the claims of the '331 patent should be allowed, repeatedly cited the "surprising discovery" throughout the prosecution of the patents in suit, highlighted the discovery in numerous parts of the specifications of the patents in suit and, in fact, the patent examiner explicitly allowed the claims of the *'042 patent* due to Purdue's discovery of the reduced dosage range. As such, Purdue cannot in [*87] good faith contend that it did not know that this "discovery" - and any information that it did not have scientific proof to support this discovery - was material information. Purdue's own scientists and experts testified that Purdue did not have any scientific proof of the "discovery" until analyzing the NDTI data recorded from 1996 to 2001. Clearly, Purdue should have informed the PTO that its discovery - whether termed a "discovery," "insight," a "result," an "expectation," or a "theoretical argument" - had not been proven and was "inherently difficult to demonstrate." DX 3629. These repeated intentional material misrepresentations are so serious as "to warrant the severe sanction of holding the patent[s] unenforceable." *Hoffmann-La Roche, 323 F.3d at 1372*.

As this Court has found that Purdue committed inequitable conduct before the PTO during the prosecution of the '331, '912, '295 and *'042 patents*, the patents in suit - the '912, '042 and *'295 patents* - are rendered unenforceable. See *Hoffmann-La Roche, 323 F.3d at 1372*; *Lummus Indus., Inc. v. D.M. & E. Corp., 862 F.2d 267, 274 (Fed. Cir. 1988)* ("The principle is well settled [*88] that if inequitable conduct is established as to any [patent] claim, all claims of the patent are rendered unenforceable."). [15]

15 Since the patents are unenforceable, this Court will not address Endo's other affirmative defenses against Purdue's infringement claims.

IV. Conclusion

For the reasons set forth above, this Court finds that Purdue has proven by a preponderance of the evidence that Endo infringed Purdue's '912, '042 and *'295 patents*, but Endo has proven by clear and convincing evidence that those patents are invalid due to Purdue's inequitable conduct before the PTO during the prosecution of the patents in suit. The patent claims against Endo are dismissed, patents 5,549,912,5,508,042 and 5,656,295 are declared invalid and Purdue is enjoined from enforcing those patents.

Dated: January 5, 2004

SO ORDERED:

Sidney H. Stein, U.S.D.J.